Global developmental delay and postnatal microcephaly: Bainbridge-Ropers syndrome with a new mutation in *ASXL3*☆,☆☆

Retraso global del desarrollo y microcefalia posnatal: síndrome de Bainbridge-Ropers con una nueva variante de novo en *ASXL3*

Dear Editor:

Exomic sequencing reveals genetic syndromes in up to 25% of subjects with genetic diseases which remain undiagnosed after multiple genetic studies.[1,2] In 2013, Bainbridge and Ropers reported de novo variants of truncating mutations of the *Additional sex combs-like 3* gene (*ASXL3*, locus 18q12.2, 12 exons) in 4 patients with severe psychomotor retardation, and learning and feeding difficulties.[3]

We examined a 3-year-old boy, who was the fourth child of healthy, non-consanguineous Mexican parents. The other 3 children were healthy. He was delivered vaginally after a normal, full-term pregnancy (length: p > 97; weight: p > 85; head circumference: p97; Apgar score: 7.9). He achieved head control at 6 months and could sit at one year. At 36 months of age, the patient presented severe neurodevelopmental delay and was unable to speak or walk. He also presented microcephaly (−4.35 SD), short stature (−3.5 SD), and poor weight gain (−4.6 SD). The facial phenotype included prominent forehead, hypertelorism, high anterior hairline, thin eyebrows, mild synophrys, anteverted nostrils with hypoplastic alae nasi, high-arched palate, and low-set prominent ears. We also observed fingertip pads, broad thumb and big toe in both hands and feet, and cryptorchidism (Fig. 1). A brain MRI scan revealed cortical atrophy. Karyotyping (46, XY) and comparative genomic hybridisation (400k) yielded normal results. Baylor Miraca Genetics Laboratories performed whole exomic sequencing from purified genomic DNA extracted from the patient's peripheral blood. Sequencing consisted in DNA fragmentation by sonication and ligation with multiplex sequencing adapters on the Illumina platform.[4] The process of enrichment/capture was performed by hybridisation of a microarray customised by NimbleGen (VCRome 2.1),[5] as well as additional probes for 3650 Mendelian and mitochondrial genome genes.[6] We used the Illumina HiSeq 2000 system for analysis (median exome coverage, 95%; median

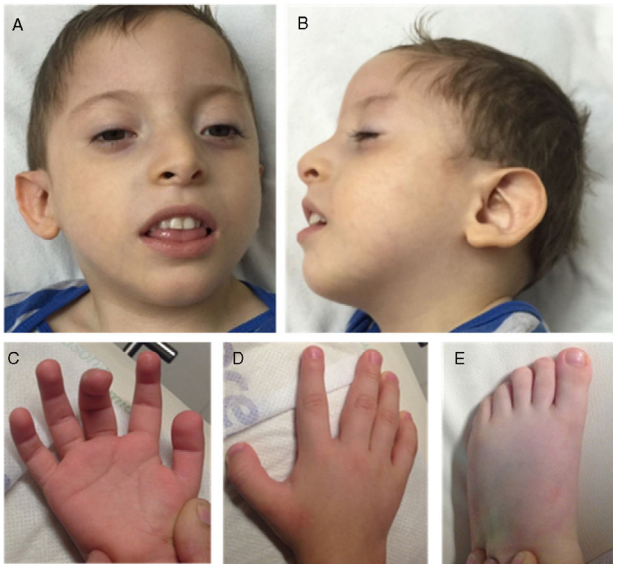

Figure 1 Clinical phenotype: (A and B) Wide forehead, prominent metopic ridge, permanently open mouth, and low-set ears with posterior rotation. (C) Fingertip pads. (D and E) Broad fingers and toes, especially the thumb and toe.

nucleotide coverage, >100×). Variant calling and annotations were performed using the Atlas-SNP/SNP-anno and Atlas-indel/HGSC-anno tools, developed in-house by Baylor College of Medicine. De novo variants and in silico predictions of nonsense changes were reported according to the American College of Medical Genetics criteria.[7] The patient was heterozygous for a 4-bp deletion on chromosome 18:31320359 at NM_030632.2 (*ASXL3*): c.2992-2995del, p.(E998fs) in exon 11; this frameshift mutation causes an aberrant protein, predicted to be deleterious. Sanger sequencing of the *ASXL3* gene in the patient's parents yielded normal results; therefore, we believe this to be a de novo variant in the proband.

Few patients with Bainbridge-Ropers syndrome (MIM #615485) have been reported to date. Diagnosis is achieved after whole-genome and exome sequencing, since the phenotype is subtle and variable.[3,8–11] The common clinical characteristics (severe psychomotor retardation, facial dysmorphism, growth failure, and feeding difficulties) can be misinterpreted as such other syndromes as Bohring-Opitz syndrome (MIM #605039) (Table 1).[12,13] Bohring-Opitz syndrome is related to genetic variants of *ASXL1*, and no variants of *ASXL3* have been detected; these syndromes are therefore considered 2 distinct entities.[3,12] Most of the described variants of *ASXL3* are de novo mutations producing premature stop codons or shifting the reading frame in the coding region of the *ASXL3* gene, and group together in a region of exon 11.[3,8,9] Bainbridge-Ropers syndrome represents a challenge for molecular diagnosis based on the analysis of a single gene or multiple-gene panel testing; therefore, the recent introduction of whole-genome or exome sequencing techniques is useful for research into the aetiology of neurodevelopmental disorders.

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Table 1 Comparison of the clinical characteristics of patients with Bainbridge-Ropers syndrome with variants of the *ASXL3* gene and patients with Bohring-Opitz syndrome.

Phenotype	Bainbridge et al.[3] (2013), Dinwiddie et al.[8] (2013), Hori et al.[10] (2016), Srivastava et al.[11] (2016)	Present study	BOS, Hastings et al.[12] (2011)
Prenatal			
Intrauterine growth restriction	5/9	No	11/14
Neurological			
Global developmental delay	9/9	Yes	14/14
Hypotonia	8/9	Yes	7/14
Feeding difficulty	8/9	Yes	14/14
Language delay	6/9	Yes	—
Seizures	2/9	Yes	—
Craniofacial			
Microcephaly	5/9	Yes	14/14
Prominent forehead	5/9	Yes	—
Arched eyebrows	5/9	Yes	—
Hypertelorism	1/9	Yes	9/14
Anteverted/hypoplastic nostrils	6/9	Yes	8/14
Low-set ears with posterior rotation	6/9	Yes	8/14
Typical BOS posture	0/9	No	14/14

BOS: Bohring-Opitz syndrome.

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Intraneural ganglion cyst of the external popliteal sciatic nerve: A possible cause of foot drop☆

Ganglión intraneural del nervio ciático poplíteo externo. Una posible causa de pie caído

Dear Editor:

Intraneural ganglion cysts are very infrequent benign lesions generally affecting peripheral nerves, particularly the external popliteal sciatic (EPS) nerve. They may cause symptoms of neuropathic pain, frequently manifesting as paralysis of the EPS nerve, which requires differential diagnosis from such other conditions as trauma, spinal compression syndrome, or lumbar disc or tumour lesion.[1] Early diagnosis is equally necessary, since delayed diagnosis leads to axonal injury, which may cause muscle denervation.[2] In the case of the tibialis anterior and fibularis longus and brevis muscles, which are responsible for foot dorsiflexion and eversion, denervation may be irreversible. Since the first description of an intraneural ganglion cyst of the SPE in 1809, pathophysiology and the different treatments proposed have constantly been debated; treatments were based on irregular clinical findings and high recurrence rates. The most widely accepted theory, Spinner's[3,4] unifying articular theory, was proposed in 2003. According to this theory, the ganglion cyst arises from the superior tibiofibular joint; the cyst allows fluid to infiltrate the articular branch of the EPS nerve, to which it is connected, and through a one-way valve mechanism, that mucinous content fills and dissects the nerve in a proximal direction.[5–7] The clinical findings constitute the most conclusive aspect of this theory, revealing decreased recurrence rates after procedures for ligating and disconnecting this articular branch were introduced into surgical treatment.[8–11]

We present a series of 2 cases of intraneural ganglion cyst of the EPS nerve and describe the patients' clinical and neuroimaging manifestations, treatment, and outcomes. We also review the literature on the subject.

Case 1

The patient was a 52-year-old man with no relevant medical history. He visited the hospital due to a 4-month history of decreased sensitivity of the right instep and the outer surface of the leg, together with steppage gait. Examination revealed loss of strength (2/5) on dorsiflexion and hallux extension of the right foot, lack of lower back pain on palpation, and deep tendon reflexes. Tinel test on the EPS nerve at the level of the head of the fibula yielded negative results. A neurophysiological study revealed chronic axonal neuropathy of the right EPS nerve. The electroneurography showed diminished motor conduction speed of the EPS nerve in the section between the popliteal fossa and the head of the fibula, as well as decreased motor and sensory potential amplitude in the superficial peroneal branch. The electromyography revealed no acute denervation (spontaneous activity) in the tibialis anterior and fibularis longus muscles, with signs of chronic reinnervation, and motor unit action potentials of increased amplitude, duration, and polyphasia. An MRI scan showed a multilobular mass measuring 2 cm adhering to the head of the fibula, and atrophy of the anterior tibialis muscle due to denervation; these findings are compatible with malformation or arthrosynovial cyst (Fig. 1A and B). An ultrasound revealed an avascular anechoic tubular structure of cystic content inside the EPS nerve, compatible with an intraneural ganglion cyst arising from the superior tibiofibular joint.

Case 2

The patient was a 53-year-old man with no previous trauma or relevant personal history, who visited our hospital due to a 6-week history of foot drop and paraesthesia of the left lateral leg, which he believed to be due to work overload. Baseline examination revealed a soft tumour which was palpable at the level of the head of the fibula; Tinel sign was positive at that point. Muscle strength was 2/5 in the anterior tibialis muscle and 3/5 in the extensor hallucis longus muscle. A neurophysiological study revealed acute axonal neuropathy of the left EPS nerve. Electroneurography findings were consistent with those of case 1, whereas

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